

## Albumin. Its place in critical care practice

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Most critically ill patients have a common pathophysiological process. Infection, trauma, or major surgery initiates an inflammatory cascade leading to the release of various inflammatory mediators (for example, cytokines) and activation of leukocytes. This is a self-perpetuating cascade, which results in damaged endothelial integrity, increasing microvascular permeability and promotes extravasations of fluids (including albumin) into the tissue. Moreover, there are several reasons why albumin supplementation might make things worse for critically ill patients.<sup>1</sup> Cost containment is becoming an increasingly important factor in medical decision making. Human albumin solutions are more expensive than other colloids and crystalloids. An acceptable alternative to albumin would be favorable. The impact of albumin infusion on survival has long been a subject of debate and several investigations. It is very difficult to comment on the rational of use of albumin in clinical practice. Variations in patients, targets, additive therapy, and other factors make interpretation of the literature difficult. Interestingly, despite advice not to use albumin, use of this product continues. There is no convincing data justifying administration of albumin either for treating hypovolemia or for correcting hypoalbuminemia. In this report, we will summarize what the literature states on the use of albumin for the critically ill patient.

Despite a growing body of systematic reviews and evidence based medicine analyses, the safety profile of albumin is still under dispute. Two meta-analysis of randomized trials have broadly assessed the effects of albumin on survival.<sup>2,3</sup> None showed a significant overall survival benefit. Indeed, the Cochrane Injuries Group Albumin Reviewers meta-analyses even indicated increased mortality amongst albumin recipients (6.8%). A major limitation of both meta-analyses is the reliance on survival as the end point. More than half of the included randomized trials were not designed to assess this end point. Another meta-analysis included only studies using purified albumin and a wide spectrum of patients. It included 55 trials involving 3,504 patients. Overall, this analysis detected no difference in mortality between patients treated with albumin and other fluids.<sup>4</sup> A more recent systematic review included 79 randomized trials with a total of 4,755 patients.<sup>5</sup> It showed definite beneficial effects of albumin in both cardiac and non cardiac surgery.

They analyzed the use of albumin administration in diverse clinical settings, such as hypoalbuminemia, ascites, sepsis, burn patients and outcomes after brain injury. They concluded that albumin does bestow benefit in terms of decreased morbidity in a wide array of clinical settings. However, the optimal dose and administration schedule for albumin remain to be delineated. Further investigations are warranted to address these issues.

The Saline versus Albumin Fluid Evaluation (SAFE) study is the largest ever multicentric, double blind, randomized controlled trial of SAFE for fluid resuscitation of critically ill patients in intensive care from 16 intensive care units in Australia and New Zealand over an 18 month period. Of the 6,997 patients who underwent randomization, 3,497 were assigned to receive 4% albumin and 3,500 to receive saline.<sup>6</sup> There were 726 deaths in the albumin group compared to 729 deaths in the saline group (relative risk of death, 0.99; 95% confidence interval: 0.91-1.09;  $p=0.87$ ). The 2 groups of patients had a similar proportion of new single-organ and multiple-organ failure ( $p=0.85$ ). There were no significant differences between the groups in the mean numbers of days spent in the ICU, days spent in the hospital, days of mechanical ventilation, or days of renal-replacement therapy. Subgroup analysis of the albumin-treated group revealed a trend towards decreased mortality in patients with septic shock, and a trend towards increased mortality in trauma patients, especially those with traumatic brain injury. This study had conclusive evidence that 4% albumin is as safe as saline for resuscitation, although no overall benefit of albumin use was seen. The commonly used higher albumin concentrations require rigorous evaluation in clinical trials.

The Cochrane Injuries Group Albumin Reviewers continuously publishes an update of the original meta-analysis. Their last search was updated in August 2004.<sup>7</sup> The conclusion was that there is no evidence that albumin reduces mortality when compared with cheaper alternatives such as saline in critically ill patients with burns and hypoalbuminemia or hypovolemia (Table 1). Very recently, Vincent et al<sup>8</sup> looked at the effect of albumin administration on morbidity (including death) in acutely ill hospitalized patients. In their meta-analysis, they analyzed a nonselective, transparent large data sampling of 71 trials. They concluded that albumin reduces morbidity in a broad category of acutely ill hospitalized patients. To make a recommendation from this study, one needs to study the data carefully, as the median duration of follow-up for all included trials was only 4 days. Also, the number needed to treat to avoid one complication was 44 patients. Using such costly therapy in this meta-analysis, there was no evidence that this was

**Table 1 -** Cochrane Database Systematic Review result on albumin use in critically ill patients from 32 trials (updated August 2004)\*:

Patients category	Relative risk of death	95% Confidence interval
Hypovolemia	1.01	0.92 - 1.1
Burns	2.4	1.11 - 5.19
Hypoalbuminemia	1.38	0.94 - 2.03
*The pooled relative risk of death with albumin administration was 1.04.		

translated to a better outcome in terms of shorter ICU/hospital stay or hospital discharge. Furthermore, the albumin used by the trials included varied from 2-25% albumin concentration. Although they calculated the total amount of albumin received in grams, the question remains whether it is the concentration of albumin preparation used, the target serum albumin level or the total grams of albumin received, that matters? Albumin has been used for over 50 years for fluid resuscitation in the ICU, despite the lack of any adequately powered randomized clinical trials. As yet, there is no evidence to support the widespread use of albumin. There is no convincing data justifying administration of albumin either for treating hypovolemia or for correcting hypoalbuminemia. Until convincing data pro albumin is presented, injudicious use of albumin is not to be recommended. Further trials are required to form optimal fluid regimens, and indications. That use of albumin in critically ill patients should urgently be reviewed by the critical care practitioner. It should not be used outside the context of rigorously conducted randomized controlled trials.

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## Use of adrenaline as an adjunct to local anesthetic agent. A cause of concern for the anesthesiologist

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Adrenaline is an endogenous catecholamine. It is a sympathomimetic agent that has both and adrenergic effects. Physicians mainly use it as a bronchodilator, during cardiopulmonary resuscitation and in the treatment of acute anaphylactic reactions. We often use adrenaline in a concentration of 5 µg/ml (1:200,000) to reduce blood flow and slow the rate of absorption of the local anesthetic agent, thus reducing the plasma concentration and prolonging the duration of action.<sup>1</sup> It has been recognized for a long time that halothane and, to a lesser extent, other volatile anesthetics sensitize myocardium to the arrhythmogenic effects of adrenaline. Sensitization is the interaction between volatile anesthetics and catecholamines that leads to reductions in the threshold for both atrial and ventricular arrhythmias. Sequentially escalating doses of adrenaline produce premature ventricular contractions and sustained ventricular tachyarrhythmias during halothane anesthesia. Pretreatment with thiopentone attenuates halothane-adrenaline induced arrhythmias, presumably via effects on the atrioventricular node or the upper bundle of His. The doses of adrenaline required to produce ventricular arrhythmias during desflurane or sevoflurane anesthesia are similar to, but significantly less than those observed during administration of isoflurane and halothane.<sup>2</sup> However, Katz and Katz<sup>3</sup> made 3 suggestions for

**Table 1** - Studies showing potentially serious hemodynamic side effects of ADR when used as an adjuvant to LDC among patients undergoing various surgical procedures.

Author and reference	Year	Drug combination	Composition	No. of patients	Side effects (%)
Pasternak et al <sup>4</sup>	2004	LDC + ADR	--	100	Arterial hypertension (58%)
Murthy and Rao <sup>5</sup>	2001	<b>5 Groups</b>		112	
		LDC	LDC-0.5% (Control)	20	No significant hemodynamic changes
		LDC + ADR	LDC-0.5%, ADR 1:200,000	23	Biphasic hypotension
		LDC + ADR	LDC-0.5%, ADR 1:100,000	24	Biphasic hypotension
		N. saline + ADR	NaCl-0.9%, ADR 1:200,000	23	Diastolic hypertension
		N. saline + ADR	NaCl-0.9%, ADR 1:100,000	22	Severe tachycardia
Phillips et al <sup>6</sup>	1993	<b>4 Groups</b>		80	
		LDC	LDC-0.5% (Control)	-	No significant hemodynamic changes
		LDC + ADR	LDC-0.5%, ADR 1:200,000	-	Hypotension (55%)
		N.Saline	NaCl-0.9% (Control)	-	No significant hemodynamic changes
		N. Saline + ADR	NaCl-0.9%, ADR 1:200,000	-	Hypotension (40%)
LDC - Lidocain, ADR - adrenaline, N. saline - normal saline, NaCl - sodium chloride					

clinical precautions that have stood the test of time. 1. We should only use solutions of adrenaline of 1:100,000-1:200,000. 2. The dose in adults should not exceed 10 ml of 1:100,000 adrenaline in any 10-minute period. 3. The dose in adults should not exceed 30 ml of 1:100,000 adrenaline in any given 60-minute period. The Ear Nose and Throat, Plastic, Dental and Neurosurgeons mainly use adrenaline mixed with lidocaine. Different studies have revealed that ranges of hemodynamic changes occur by the addition of adrenaline to either lidocaine or normal saline (**Table 1**).<sup>4-6</sup>

In a study conducted by Murthy and Rao<sup>5</sup> among 5 groups, 4 groups of patients developed significant hemodynamic changes irrespective of mixtures and the concentrations of adrenaline used. Likewise, in another study conducted by Phillips et al.<sup>6</sup> among the 4 groups, 2 of the study groups of patients developed significant hypotension, unlike the control groups when they mixed adrenaline with lidocaine and normal saline. Moreover, in tumescent anesthesia where the volume of the local anesthetic mixed with adrenaline is relatively more, it poses a greater threat to the development of potentially fatal cardiovascular responses, as the likelihood of exceeding the maximum dose of adrenaline increases further.

These hemodynamic changes are typically transient, and pretreatment with metoprolol (1 mg, IV) has been effectively used to alleviate the adverse cardiovascular responses to adrenaline infiltration.<sup>7</sup> Nonetheless, they may often be life threatening.<sup>4-6</sup> Currently in the literature, there is a lack of reliable information on measures to prevent or effectively counteract these adverse effects of

adrenaline. However, clinical acumen and awareness of the committed anesthesiologists will be the key in prevention and finding an apt solution to this seemingly insignificant yet, potentially hazardous problem.

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## Spontaneous rupture of the ovarian artery following spontaneous vaginal birth

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**H**emorrhage from ruptured ovarian vessels is an extremely rare but life-threatening complication during pregnancy.<sup>1</sup> These are very few earlier reported cases on postpartum ovarian artery rupture after delivery.<sup>2-3</sup> We describe a patient with spontaneous ovarian artery rupture 5 hours after delivery.

A 30-year-old woman, gravida 5 para 5 (G5P5) was referred to the Obstetrics Department with the complaint of diffuse abdominal pain and minimally vaginal bleeding 5 hours after delivery. The pain was associated with nausea and vomiting. Her antenatal course was uneventful, and past obstetric history included a previous cesarean section followed by 3 normal vaginal births no systemic illness. On physical examination, she seemed to be in moderate distress secondary to abdominal pain. The body temperature was 37°C, heart rate was 110 beats/min, respiratory rate was 20 breaths/min, and blood pressure was 90/60 mm Hg. Abdominal examination revealed diffuse and rebound tenderness. Pelvic examination revealed a tender uterus with a post delivery open cervix and minimal vaginal bleeding. The attending radiologist performed ultrasonographic examination, which revealed a normal liver and spleen. Perihepatic and perisplenic, an amount of free fluid was visible in the abdomen. Her hematologic workup demonstrated hemoglobin =8.38 g/dl (normal range [NR]: 12.3-15.3 g/dl), hematocrit=4.1% (NR: 37.7-53.7%), white blood cell=1300 (NR: 4.4-11.3 uL), platelet counts=385,000 x 10<sup>3</sup>/ul (NR: 142-424 uL). Hemoglobin level gradually decreased and she seemed to enter a state of shock. We performed emergency explorative laparotomy with a suspicion of uterine rupture. After opening the peritoneum approximately 1500 ml blood was aspirated. There was no retroplacental hematoma. Further inspection of uterus, tubes, and ovaries were normal. The liver, spleen, stomach, gallbladder, and intestines showed no signs of bleeding. Closer inspection showed the spontaneous rupture of left ovarian artery, which was bleeding. Left ovarian artery was sutured primarily and we observed no further bleeding. After operation she was referred to their intensive care unit in a stable condition. She was transfused with 5 units of blood intra- and postoperatively, and as the postoperative

course was uneventful, she was discharged home on the 4th day of admission.

Hemorrhage from ruptured ovarian vessels is a rare but life-threatening complication during pregnancy.<sup>1</sup> Mojab and Rodriguez,<sup>2</sup> and Ginsburg et al<sup>3</sup> discussed postpartum ovarian artery rupture with retroperitoneal hemorrhage and post-partum spontaneous rupture of a branch of the ovarian artery. The clinical manifestation is mostly abdominal pain with hemodynamic collapse. Laboratory findings show a decrease of hemoglobin and hematocrit levels. Ultrasound examination demonstrates free fluid in the abdomen. At the beginning after delivery she had no signs of hemodynamic instability. The blood loss developed slowly and the level of hemoglobin decreased gradually; the young patient could adjust to the decreasing circulating volume of blood. Finally, she began to show signs of hemodynamic instability. The treatment consists of preoperative hemodynamic stabilization of the patient and urgent laparotomy. Rupture of uterus, uterine artery, utero-ovarian vessels, adrenal-gland vein, splenic vein, renal arterial aneurysm, kidney, liver or spleen should remain in differential diagnosis.<sup>3</sup> Cardiac output, heart rate, blood volume increases, and hormonal factors may impair the arterial wall and additional stress such as delivery may result in the spontaneous rupture of ovarian artery.<sup>4</sup> Structural changes in intima and media of the arterial wall are demonstrated during pregnancy. The observed hyperplastic intimal changes are histologically equivalent with the changes that appear with hypertension and oral contraceptive use.<sup>5</sup> All these changes during pregnancy may contribute to the etiology of spontaneous ovarian artery rupture following spontaneous vaginal birth. It is still controversial whether the arterial wall weakens during pregnancy and additional stress such as delivery or previous cesarean section may cause spontaneous rupture of ovarian artery.

Spontaneous rupture of an ovarian artery after delivery is an extremely rare complication. One must think about it in cases of diffuse abdominal pain and hemodynamic collapse. The treatment consists of performing a laparotomy with suturing of the ruptured ovarian artery.

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## Two anatomic variations in the arm related to the median nerve

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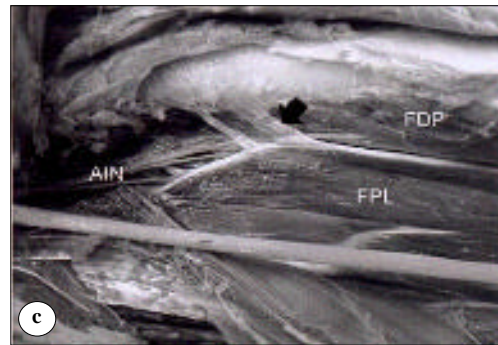
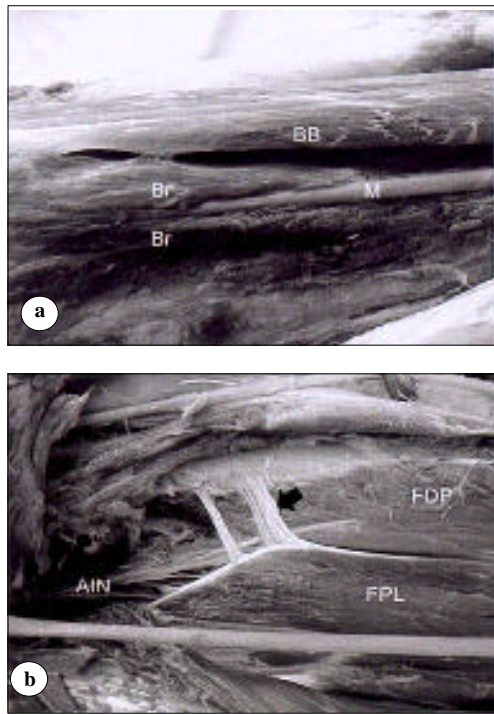
Disorders of the peripheral nervous system are quite common; of these disorders entrapment neuropathies are frequently encountered by the clinician. The term entrapment neuropathy implies that the nerve is compressed by adjacent anatomic structures.<sup>1,2</sup> Distribution of the median nerve in the arm is rarely subjected to variation, but there are numerous reports regarding median nerve compression. Variations of the nerve and the adjacent structures may be seen clinically or observed during surgery, autopsy or cadaveric dissection. We recently encountered 2 anatomic variations that can possibly cause entrapment neuropathy of the median nerve during our routine cadaver dissections. Typically, the median nerve receives fibers from C6, C7, C8 and T1 spinal nerves and supplies motor, sensory and sympathetic nerve fibers to the upper limb. In the arm, its course is closely related to the brachial artery. Along with the brachial artery, it travels between the brachialis (Br) and the medial intermuscular septum in the arm until it reaches the nerve and the cubital fossa, which has no branches. Sometimes a small branch to the brachial artery can be seen. At the distal

humerus, both nerve and artery pass through the antecubital fossa underneath a fibrous sheath and the bicipital aponeurosis, which takes origin from the biceps tendon and the fascia of the flexor-pronator mass. It then passes between the 2 heads of the pronator teres. In this muscle, the largest branch can be found, the anterior interosseous nerve. The nerve continues in the forearm between the flexor digitorum profundus and flexor digitorum superficialis.<sup>2</sup>

We encountered 2 anatomic variations that can cause entrapment neuropathy of the median nerve during our routine student dissections. In one of our dissections, we encountered a variation of the median nerve at the level of the Br. The cadaver was a 47-year-old male and has no visible scars or wounds on both upper extremities. Normally, the median nerve courses in the groove between the biceps brachii (BB) and Br.<sup>2</sup> The median nerve can be compressed above the elbow due to an accessory tendon, which arises from the Br in 10% of the cases. According to some authors, the muscle fibers arise from the Br connect to some of the fibers of BB and end in bicipital aponeurosis and compress. In this case, which is located in the arm, at 9 cm proximal to the medial epicondyle, the nerve leaves the brachial artery and passed through the antecubital fossa piercing the Br (**Figure 1a**). The course of the median nerve on the other arm was normal. In another dissection, we encountered an abnormal pattern of the accessory head of flexor pollicis longus (FPL) (Gantzer's muscle). The cadaver was a male with unknown age with no visible scars or wounds on both upper extremities.

Gantzer's muscle is the accessory head of the FPL, which usually originates from medial epicondyle or processus coronoideus and lies on the ulnar side of the FPL. It has been implicated as one of the causes of the anterior interosseous nerve (AIN) compression in the proximal forearm.<sup>1,3-5</sup> The anterior interosseous nerve is the largest branch of the median nerve in the forearm and has no sensory fibers.<sup>2</sup> The incidence of the Gantzer's muscle was reported between 45-74%.<sup>3-5</sup> The difference of these ratios might be due to the fact that the muscle can be fused with some of the superficial flexor group and can be overlooked during dissection. The muscle usually passes between the superficial branch of the median nerve and the anterior interosseous nerve; but rarely passes superficially to both of the nerves.<sup>2</sup>





**Figure 1** - Photograph showing: (a) Right arm, elbow. BB - biceps brachii, Br - brachialis, M - median nerve. The figure shows the median nerve piercing the brachialis muscle. (b) Left arm, distal of the elbow joint deep compartment, supination. FDP - flexor digitorum profundus, FLP - flexor pollicis longus, AIN - anterior interosseal nerve, Black arrowhead: Gantzer's muscle seen as 2 tendinous slips. The figure shows the accessory head of the flexor pollicis longus in supination. (c) Left arm, distal of the elbow joint deep compartment, pronation. FDP - flexor digitorum profundus, FLP - flexor pollicis longus, AIN - anterior interosseal nerve, Black arrowhead: Gantzer's muscle seen as 2 tendinous slips. The figure shows the accessory head of the flexor pollicis longus in pronation.

The most frequent site of origin of the muscle has been reported to be the medial epicondyle of humerus, a well-developed connecting fascia made up of the intermuscular septa among the pronator teres and flexor muscles in the proximal forearm, flexor digitorum superficialis and both the medial epicondyle and coronoid process.<sup>3-5</sup> However, the most frequent site of the origin of the muscle has also been reported to be the coronoid process in 87.5%. In the forearm the muscle ends in the ulnar part of the FPL or ends in 2 tendinous slips, one of which connects to FPL, whereas the other coursed to join the tendon of the flexor digitorum profundus (FDP) to the index finger.<sup>3-5</sup> Although the accessory head of the FPL is not a rare variation,<sup>3-5</sup> in our dissection the accessory head was seen as 2 tendinous slips clearly different that have been reported and course of these slips were extremely different from the cases in the literature. It turns to the radial side and fuses to the FPL immediately after its origin, and it seemed to compress the anterior interosseous nerve strongly especially when the forearm is in supination (**Figure 1b**). When the forearm is in pronation there is no significant effect on the nerve (**Figure 1c**).

In this study, we report 2 anatomic variations that are responsible for entrapment neuropathies of the median nerve. These variations must be kept in

mind by orthopaedic surgeons dealing with the surgical interventions and release operations related to the entrapment neuropathies of the upper extremity.

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## Sex determination using sex determining region Y primers by single conventional polymerase chain reaction

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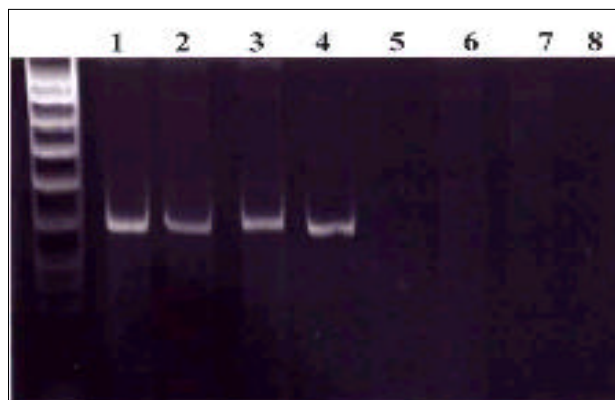
The development of the polymerase chain reaction (PCR) as a means of amplifying known sequences of DNA allows determination of gender by amplification of sequences unique to the Y chromosome. Detection of Y-specific sequences has clinical importance as it would be useful in fetal gender identification in mothers who are carriers for X-linked disorders and in forensic medicine.<sup>1</sup> There were reports dealing with sex determination to detect Y-specific sequences by PCR. Established PCR-based on sex determination methods using the X-Y homologous region of the amelogenin gene,<sup>2</sup> the Y chromosome specific sequences include the Y-specific repeat sequences, DYS14,<sup>3</sup> and the sex determining region Y (SRY).<sup>4</sup> One study used a nested PCR using SRY forward/reverse as external primers and SRY-5'-nested/3'-nested as internal primers<sup>5</sup> for detection of Y-specific sequences. The difficulties with the nested PCR prompted us to develop a single conventional PCR by cross-using the SRY forward/SRY 3'-nested primers.

We prepared genomic DNA from the peripheral blood samples collected from adult males and females in EDTA-containing tubes. Cell-free DNA from plasma to plasma by using QIAamp DNA blood Mini Kits (Qiagen, UK) according to the blood and body fluid protocol with minor modifications. Primers for amplification of 173 bp sequence are as follows:

SRY forward: 5'GTG TCC TCT CGT TTT GTG  
AC 3,

SRY 3'-nested: 5'CTA GTA CCC TGA CAA TGT  
ATT C 3'.

We performed PCR amplification in a total volume of 25 µl containing extracted DNA, 200 µM dNTPs, 20 pmol of each primer, 1 x Taq polymerase buffer (containing 1.5 mM MgCl<sub>2</sub>), and 1 U of Taq polymerase (Roche Biochemicals). The thermal cycling began with denaturation at 94°C for 7 minutes, followed by 40 cycles of 94°C for 30 seconds, 55°C for 30 seconds, and 72°C for one minute, with final incubation at 72°C for 12 minutes. The PCR amplification products were separated by 8% acrylamide gel electrophoresis and



**Figure 1** - Photograph of electrophoresed polymerase chain reaction products of 4 males and 3 females genomic DNA. Lane 1 represent molecular weight marker VIII (pUCBM21 DNA cleaved by Hpa II, Dra I and Hind III). Lane 2, 3, 4 and 5 represent male DNA. Lane 6, 7 and 8 represent female DNA.

visualized by exposure to ultraviolet light after ethidium bromide staining. A female staff member performed all procedures including blood specimen collection and preparation, DNA extraction and PCR amplification. To determine the specificity of male genomic DNA in a single PCR using SRY forward / SRY 3'-nested primers; we examined 15 male genomic DNA and 15 female genomic DNA samples. All the male samples were positive and produced a 173 bp fragment while the 173 bp fragment was not detectable in the female samples (**Figure 1**). We amplified all female samples giving negative results for the Factor VIII gene, as a positive control (data not shown). To evaluate the sensitivity of the developed assay, we applied the single PCR, using SRY forward/SRY 3'-nested primers, to serial dilutions of 220 ng of male genomic DNA in female genomic DNA. Positive signals were detected up to the 1/10000 dilution, which is almost at the 3 cells level (data not shown).

We developed a new single PCR of a nested PCR for sex determination, which is able to identify Y-specific signals with no false-positives and false-negatives. Honda et al<sup>5</sup> developed a single PCR by use of the internal pair of primers used in the nested PCR devised by Lo et al.<sup>3</sup> This study is an attempt to cross-use one primer from the external pair of primers and another from the internal pair of primers of a nested PCR to develop a single PCR. Although this method is incomparable to real time quantitative PCR, it has overcome the difficulties of nested PCR and provided a feasible methodology with an acceptable specificity and sensitivity. However, the sensitive nature of this assay, which can detect copies at the 3 cells level, implies that great care must be taken to avoid contamination.

Due to the sensitivity of this method it could potentially be used for prenatal sex identification using free fetal DNA in maternal plasma or serum in addition to chorionic villous samples. Therefore, considering the sensitivity of the assay, it could be used in parallel with other Y-specific assays to increase the certainty of the results.

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## Serum calcium and phosphorus levels in patients with ischemic heart disease

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**I**shemic heart disease (IHD) is estimated to be the leading cause of lost life years until at least 2020.<sup>1</sup> There is a long list of well known risk factors for cardiovascular diseases but limited work has been carried out on the relation of serum calcium and phosphorus levels with IHD, and their results are controversial. Calcium is a vital electrolyte, in normal adults plasma level ranges from 2.2-2.6 mmol/l (8.8-10.4 mg/dl). Plasma concentration of phosphorus is normally 2.5-4 mg/dl. In a case control study of men in Finland with 10 years follow up, there were no significant differences in concentrations of serum calcium, and serum

magnesium between cases who died from cardiovascular diseases and controls.<sup>2</sup>

Jorde et al<sup>3</sup> shows that total serum calcium is a predictor of cardiovascular disease in men. We performed this cross-sectional study in order to compare the status of total serum calcium and phosphorus levels in patients with coronary artery disease (CAD) with normal controls. We used a questionnaire for demographic data and we excluded patients with malignancy, renal failure (creatinine >1.5 mg/dl), liver diseases, digestive disorders, hyperthyroidism, and those undergoing treatment with thiazide diuretics. We collected blood samples for measurement of serum total calcium, phosphorus, urea, creatinine, triglyceride, uric acid, cholesterol and fasting blood sugar after overnight fasting, and we determined biochemical parameters with ordinary kits using RA 1000 apparatus.

The patients underwent routine coronary angiography using optimus-M 200 Philips angiography system. The number of the vessels with significant stenosis (>50%) was detected by a cardiologist who was not aware of the investigation. Stenosis less than 50% was known as non-significant lesions and were excluded. We analyzed all data through EPI info 2000 and *p* values <0.05 were considered as statistically significant, after gathering the samples and data recording in the questionnaire. We studied a total of 230 consecutive patients (149 males and 81 females) admitted for coronary angiography in Shafa Hospital. Their age ranged from 23-78 years with a mean age of  $52.8 \pm 11.2$  years, 142 (61.7%) patients had CAD (group I) and 88 (38.3%) subjects had normal coronary angiogram, as control group (group II). Single vessel disease was detected in 58 (40.8%), 2 vessel disease 33 (23.3%), and 3 vessel disease 51 (35.9%) of patients with CAD. Mean age was  $(55.1 \pm 10.2)$  years in group I,  $(47.9 \pm 11.6)$  years in group II. The mean age was significantly higher in group I (*p*<0.0001). Patients with CAD had diabetes mellitus, high blood pressure, hyperlipidemia, and smoking habitus more than control group, (all *p*-values <0.05). The mean calcium and phosphorus concentrations in the 2 groups are given in Table 1. The concentration of calcium and phosphorus did not significantly differ between patients with CAD and normal controls. Serum calcium and phosphorus levels had no significant association with the number of vessels diseased. We indicated calcium has an important role in the pathogenesis of atherosclerosis, an association between serum calcium and the metabolic syndrome.<sup>4</sup> If such an association exists, one would expect serum calcium to be related to CAD. We suggested high serum total calcium concentration to be an independent risk factor for myocardial infarction in middle aged men.<sup>5</sup> In our study, the mean levels of total serum calcium and phosphorus were not significantly different between the patients with and without



CAD, and serum calcium and phosphorus had no significant association with the angiographic severity of CAD.

Narang et al,<sup>6</sup> showed that serum phosphorus had an independent positive association with the angiographic severity of CAD. In this study, we could not measure the amount of calcium deposition in atherosclerotic plaques of patients with CAD, but regarding the unique concentrations of the total serum calcium and phosphorus between 2 groups of patients with and without CAD, our data suggests that the total serum calcium and phosphorus had no relation with IHD.

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## Blood and saliva lactate levels during recovery from supramaximal exercise

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Lactate is now recognized to be an important source of energy for skeletal muscle metabolism, measuring blood lactate concentration (samples)

provides information not only regarding changes in glycolysis, but also on anaerobic work capacity. Blood sampling involves blood loss, emotional stress and discomfort, whereas saliva is easy to collect and non-invasive. Several authors have described the possibility of evaluating the changes produced in the composition of saliva in response to exercise as a non-invasive method of determining lactate threshold.<sup>1,2</sup> There is some research, which shows parallelism between the saliva and blood lactate response during incremental exercise.<sup>2</sup> The aim of this study is to investigate whether there is a relation between lactate increase of blood and saliva, during seated recovery after supramaximal exercise.

A group of 10 male athletes, practicing an average of 6 hours of sports activities per week, and with an acceptable level of physical fitness, agreed to participate in the study after the objectives of the investigation and the protocol to be followed was explained to them. The characteristics of the participants were as follows: average age  $21.4 \pm 1.50$  years (range 21-26.5 years), height  $179 \pm 4.01$  cm (range 174-189 cm), weight  $81.7 \pm 13.30$  kg (range 65 - 100 kg), and body mass index  $25.4 \pm 4.40$  kg/m<sup>2</sup> (19.4-30.3 kg/m<sup>2</sup>). No athlete has a smoking habit. All participants followed their customary diets and performed their habitual professional and recreational activities. The time of experiment (10:00-12:00 am) was chosen to minimize the influence of circadian variations in salivary flow and composition. The test was performed at a minimum of 3 hours after breakfast and conducted in a well-ventilated room with an ambient temperature of 20-24°C, and relative humidity ranging between 40-55%. The subjects performed a Wingate anaerobic power test (WAPT) on Monark 814 E (Monark Exercise AB, Vansbro, Sweden). They warmed-up for 5 minutes at a pedaling rate of 60-70 RPM against a resistance equal to 20% of that was calculated for the subsequent WAPT. Two unloaded 5-second sprints were performed at the end of the 3rd and 5th minute of the warm-up period. The maximal pedaling rate (RPMmax) attained during the sprints was recorded. Following a 5 minute rest to eliminate any fatigue associated with the warm-up, they performed the WAPT against a resistance of 0.75 kg/kg body mass. They were instructed to pedal as fast as possible from the onset of the test. The resistance was applied when 70% of the previously recorded RPMmax was attained. They were verbally encouraged to maintain as high a pedaling rate as possible throughout the 30 second test duration. Heart rate was monitored throughout the warm-up, the test and the recovery method using a sport-

**Table 1** - The values of plasma and salivary lactate (mmol/l).

Variables	Rest	R0	R5	R15	p
<b>Blood lactate</b>					0
Median	1.7	11.7	12.7	9.45	
Min-max	(1.22-2.53)	(1.22-2.53)	(8-16.20)	(5.20-13)	
<b>Saliva lactate</b>					0
Median	0.21	0.24	0.27	0.43	
Min-max	(0.9-0.30)	(0.11-0.49)	(0.9-0.56)	(0.22-0.63)	
Rest - before warm up, R0 - immediately after exercise, R5 - 5 minutes during recovery, R15 - 15 minutes during recovery.					

**Table 2** - Percentile of lactate increases compared with resting level.

Variables	R0 (%)	R5 (%)	R15 (%)
<b>Blood lactate</b>			
Rest	(600)	(650)	(455)
<b>Saliva lactate</b>			
Rest	(14)	(29)	(104)
Rest - before warm up, R0 - immediately after exercise, R5 - 5 minutes during recovery, R15 - 15 minutes during recovery.			

Tester heart-rate monitor (Polar Electro, Kempele, Finland). The blood samples from all subjects were taken in tubes with sodium fluoride (NaF) from the antecubital region for lactate analysis, before the warm-up (rest), immediately after exercise (R0), 5 (R5), and 15 (R15) minutes following the WAPT in the inactive seated recovery period. Saliva samples were obtained at the same time with blood samples. Each subject was instructed to floss his teeth and thoroughly clean the oral cavity the night before saliva collection. Thirty minutes before the exercise test, each subject was given 500 ml of water to ensure adequate body hydration. The mouth was rinsed with deionized water immediately before saliva collection (resting or after exercise). In addition, each subject was instructed to empty his mouth of "old" saliva before spitting into a sterile container. Samples were kept at 4°C and transported to the laboratory. Once in the laboratory, samples were centrifuged and supernatants were separated and stored at -80°C. In order to reduce the variability to a minimum level and to avoid any possible interference, the clear transparent upper layer of the saliva samples was used for the lactate determination. Blood and saliva samples were analyzed using lactate PAP kit (Milchsaeure, Boehringer, Ingelheim, Germany) with a UV-Spectrophotometer (Philips Electronics, Eindhoven, The Netherlands) at the wavelength of 505 nm. Following performance of the homogeneity test; it was observed that the variances were not homogenous ( $p > 0.05$ ). While the Friedman Test was applied to compare the difference between Rest, R0, R5 and R15 measurements, Wilcoxon test was applied to determine from which groups the difference emerged. Significance level was accepted as  $p < 0.012$  by performing Bonferroni correction ( $\alpha/k$ ,  $k$ = comparison coefficient).

The differences were found significant between blood and saliva lactate values, at the measurements

taken during rest and recovery (Friedman  $p < 0.001$ ). Blood lactate increased 10 mmol (600%), 11 mmol (650%), and 7.75 mmol (455%) at R0, R5 and R15, from resting value and decreased 3.25 mmol (26%) at R15, according to R5 value (Wilcoxon,  $p < 0.012$ ). Saliva lactate indicated an increase at R0 of 0.03 mmol (14%), R5 at 0.06 mmol (29%) and R15 at 0.22 (104%) mmol compared with resting level ( $p < 0.012$ ). Plasma and saliva lactate values are presented in **Table 1**.

According to Wilcoxon test, the differences between time points of measurement are significant  $p < 0.01$ . There is no correlation between sample time values of blood and salivary lactate. The percentile of lactate increases with the sample time as presented in **Table 2**.

The study suggests that blood lactate peak occurs at the 5th minute of recovery, and saliva lactate peak occurs at 10-15th minutes of recovery.<sup>1,3</sup> Segura et al<sup>2</sup> and Chicharro et al,<sup>4</sup> found a good correlation between the concentrations of salivary and blood lactate, and they proposed the determination of lactate in saliva may be an alternative to the determination in blood at a maximum graded test on a cycle ergometer. Ohkuwa et al<sup>1</sup> cannot explain on physiological grounds why salivary lactate would significantly increase following a 400 m and 3000 m run, when compared with the basal level or whether salivary lactate concentration during recovery was significantly lower compared to blood lactate concentration, or whether the peak concentration of salivary lactate occurs later than the peak of blood lactate. One possible reason may be that salivary lactate is diffused passively through the salivary glands from the blood. At present, the origin of salivary lactate after exercise is not yet clear.<sup>1</sup>

In this study, during the post-exercise inactive recovery, plasma lactate showed an increase of 600% at R0, 650% at R5 and saliva lactate indicated

an increase of 14% at R0 and 29% at R5, plasma lactate was eliminated by 26% at R15, while saliva lactate increased by 104% at R15, compared to the resting values (**Table 2**). As can be seen, plasma and saliva lactate show different types of dynamics and there is not a linear relation between the 2. When the percentage increase of saliva lactate is compared with that of plasma lactate in our previous study as well as in present study, no relation between them is observed. However, following WAPT, saliva lactate levels at the post-exercise 15th minute in the previous and current studies were the same (0.43 mmol/l). Our results do not indicate the presence of any significant relationship between saliva and blood lactate values.<sup>5</sup>

It is expected that salivary lactate levels are parallel with plasma lactate levels with increasing workloads. Some studies suggest that determination of lactate in saliva may be an alternative to blood lactate investigation.<sup>2</sup> In both studies our plasma lactate and saliva lactate showed increases with supramaximal loading. There was no significant correlation between the peak lactate of saliva and blood increase, also percentile of lactate increases in blood and saliva, after supramaximal exercise.

In conclusion, it seems doubtful to estimate plasma lactate level by using saliva lactate level after supramaximal exercise.

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## Target level controlled sedation. An alternative to general anesthesia in endovascular treatment of intracranial aneurysms

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Controlled sedation, commonly used to describe the process of administering sedatives or dissociative agents with or without analgesics to induce a state that allows the patient to tolerate unpleasant procedures by relieving anxiety, discomfort, or pain; while maintaining independent cardio-respiratory function is a term we refer to as target level controlled sedation (TLCS).<sup>1</sup> Endovascular therapy as interventional neuro-radiology (INR) is now an established therapeutic alternative to surgical clipping of some cerebral aneurysms.<sup>2</sup> In most institutions, an anesthesiologist is involved in the care of the patient during INR treatment.<sup>3</sup> The roles of the anesthesiologist in the INR suite are to monitor the patient, to provide appropriate anesthesia to facilitate the procedure, and to manage any complication that may arise. Embolization is usually performed under general anesthesia (GA) but in our study, we evaluate TLCS using 2 different agents in the anesthetic management of patients during the treatment of their cerebral aneurysm in the neuroradiology suite.

After approval of the Institutional Ethics Committee, and obtaining informed consent; 63 American Society of Anesthesiologists (ASA) I-III patients (37-68 years old, at least one week later than their subarachnoid hemorrhage) undergoing treatment for intracranial aneurysms by Guglielmi detachable coils (GDC) embolization were enrolled for our study. Patient demographic data, and current events prior to treatment, including the neurological status of the patient and duration of the procedure were documented. We established the intravenous access in the left hand. Patients were premedicated with midazolam 0.05 mg/kg and fentanyl one mg/kg intravenously (IV), and oxygen supplementation was stated at 2 L/min via nasal cannulae. After randomization, patients received an initial dose of propofol (10 mg/ml Fresenius-Kabi GmbH, Austria) 0.5 mg/kg (group P) or midazolam (one mg/ml, Dormicum, Roche, Basel, Switzerland) 0.05 mg/kg (group M), followed by an infusion of either propofol or midazolam as a sedative agent. The infusion rate was adjusted to maintain a sedation level of "5" by Ramsey Sedation Scale. If there was movement during the procedure, patients received

additional bolus doses of propofol 0.3 mg/kg in group P, and midazolam 0.03 mg/kg in group M. After the femoral artery puncture and the initial angiogram, a 6F (2-mm diameter) nontapered guide catheter is placed in the internal carotid or vertebral artery. This guide catheter allows the passage of the microcatheter for contrast injection to perform angiograms and road mapping. Road mapping is a computer subtraction technique that allows the interventional neuroradiologist to see in real time the radio-opaque endovascular tools in superimposition with a map of the intracranial arteries.

Anticoagulation is provided with 3000-5000 IU heparin IV, followed by 1000 IU per hour. Heparinization is necessary due to the risk of thromboembolic complications. In the embolization procedure, coils of decreasing sizes were delivered into the aneurysm cavity and electrolytically detached. We recorded all complications (desaturation, apnea, hypotension, hypertension, bradycardia, tachycardia) relevant to sedation and the procedures. At the end of the procedure, the radiologist was asked to evaluate patient sedation in terms of excellent (no movement), good (one movement, no critical time), average (more than one movement or one movement at critical time) or poor (failed sedation; unable to perform procedure). Data for groups are presented as mean  $\pm$  SD. Statistical analysis was performed with Chi-square and t-tests where appropriate, a *p*-value  $<0.05$  was considered significant.

Sixty-three ruptured aneurysm patients underwent GDC embolization under TLCS. There were 38 men and 25 women with a median age of 51 years (range 37-68 years). The 2 patient groups were similar with respect to age, gender, duration of the procedure and Glasgow Coma Scale (GCS) (Table 1). The mean GCS of the patients before the procedure was  $11.4 \pm 3.3$  in group M, and  $11.9 \pm 2.7$  in group P. The duration of the procedure ranged from 89 to 213 minutes without significant differences between the 2 groups (Table 1). Coiling procedure was achieved successfully in all patients. The mean infusion rate to maintain "Ramsay Sedation Score 5" all through the procedure was  $0.03 \pm 0.02$  mg/kg/h for midazolam (group M), and  $2.9 \pm 1.4$  mg/kg/h for propofol (group P) Table 1. Two patients in group M and one in group P had decreases in oxygen saturation to less than 90% with the lowest level being 84% for more than one minute, but no adverse clinical outcome was detected as a result. Oxygen saturations normalized after increasing nasal oxygen supplementation from 2-4 L/min. Except from these 3 patients, no serious respiratory or hemodynamic complications occurred with either drug regimens. There were no other adverse events, or complications related to sedation in either groups. All patients satisfactorily maintained a level of

**Table 1** - Profile of patients undergoing GDC treatment of cerebral aneurysms.

Characteristics	Group M	Group P
No. of patients	31	32
Duration of procedure (min)	$131 \pm 41$	$157 \pm 56$
Age (year)	$49 \pm 11$	$52 \pm 15$
Weight (kg)	$75 \pm 19$	$79 \pm 21$
Male	13	12
Female	18	20
GCS	$11.4 \pm 3.3$	$11.9 \pm 2.7$
Infusion rate (mg/kg/h)	$0.03 \pm 0.02$	$2.9 \pm 1.4$
GDC - Guglielmi detachable coils, GCS - Glasgow coma scale.		

sedation that was adequate for the completion of the procedure.

Traditionally, the treatment of cerebral aneurysms involved surgical intervention,<sup>4,5</sup> but recent developments in INR have resulted in more patients undergoing endovascular coiling. There is little information in the literature regarding the anesthetic management of patients with cerebral aneurysms undergoing endovascular treatment. Our goal was to manage GDC embolization of the patients in the INR suite with TLCS. Target level controlled sedation; the less invasive approach of INR may be a good alternative in the management of embolization procedure. In addition, to reducing the risk associated with GA, performing GDC embolization under sedation permits regular neurological evaluation of the patient throughout the procedure. In the event of a thromboembolic complication, early detection of neurological deficits and their severity allows timely and appropriate use of thrombolytic therapies. The technique of anesthesia used for INR procedures varies from light sedation to GA from hospital to the hospital, but often GA is the preference of the neuroradiologist.<sup>6</sup> Another benefit of TLCS in GDC embolization of the aneurysms is; during TLCS, the patient serves as an effective overall monitor of neurological status. In INR, the ability to assess the neurological status of patients during the procedure or immediately at the end of the procedure is desirable. The maintenance of optimal level of blood pressure is also very important during these procedures. The sedative agents in TLCS also help to maintain intended mean arterial pressure during the procedure. The level of mean arterial blood pressure during the procedure in this study was similar in both propofol and midazolam groups, and we did not have any problem with the maintenance

of blood pressure or fluid management of the patients in INR, and no patients required any pharmacological agents to control their blood pressure during the procedure. Target level controlled sedation is an alternative to GA in GDC embolization of intracranial aneurysms. Monitoring standards (electrocardiogram, pulse oximetry, non invasive blood pressure, capnography, central venous lines for volume status) for anesthesia in the INR suite, is not different from the operation room.<sup>7,8</sup>

Published data suggest that oximetry effectively detects oxygen desaturation and hypoxemia in patients who are administered sedatives/analgesics, and early detection of hypoxemia through the use of oximetry during sedation decreases the likelihood of adverse outcomes.<sup>9</sup> The use of propofol or midazolam in INR suite requires the presence of an anesthetist, as the primary complication of sedation is related to respiratory or cardiovascular depression. Safety aspects such as the need for assisted ventilation in cases of apnea must be ready.<sup>10</sup> Our results suggest that the application of sedatives in TLCS may yield even better levels of safety compared with the conventional infusion of midazolam and propofol. The weakness of this study or the question of the readers may be "why the authors have not compared TLCS with GA for GDC embolization procedure?" The brief answer is; there is no information in the literature regarding the sedative management of patients with cerebral aneurysms undergoing endovascular treatment in the INR suite. And the next step of this study will be the comparison of GA versus TLCS.

In conclusion, the anesthetic management of patients with cerebral aneurysms performed using GDC embolization under TLCS appears to be feasible, and allows intra-procedural evaluation of the patient. Potential advantages of TLCS include early detection of neurological complications, decreased cardiopulmonary morbidity rates, shorter hospital stay, and lower hospital costs.

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## The frequency of skin diseases in obese children and adult Iraqi population

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**O**besity is a major health problem that is commonly associated with skin manifestations, such as acanthosis nigricans and skin tags, but unfortunately, only limited studies exist concerning this problem.<sup>1</sup> The aim of the present work is to evaluate the frequency of skin diseases among obese children and adults.

This study consists of 2 parts. **Part 1:** We took a cross-sectional sample from Basrah primary schools (urban only). We carried out the study from December 2003 to March 2004, and included 13 primary schools; 8 for boys and 5 for girls. The number of pupils in the sample was 4189; 2616 boys and 1573 girls. We used body mass index [ (BMI) = (weight [kg])/height [m]<sup>2</sup> ] to select the number of overweight and obese subjects considered for study. There were 52 obese; 34 boys and 18 girls, and 94 overweight; 56 boys and 38 girls, their ages ranged from 7-13 years. We considered 100 pupils; 60 boys and 40 girls of normal weight as the control group, comparable for age, sex and selected from the same class as the obese pupils. We carried out a full clinical and dermatological examination to establish the



diagnosis of skin diseases. **Table 1** shows the frequency of skin diseases found in the normal BMI, overweight and obese children, and we found no differences between the BMI groups for the following skin diseases: palmar peeling, pityriasis alba, macular hypopigmentation, pityriasis versicolor, and perioral hyperpigmentation.

**Part 2:** A case series descriptive epidemiological study conducted at Baghdad, Teaching Hospital, Department of Dermatology and Venereology, Baghdad, Iraq from December 2003 to August 2004. We included 100 obese cases; 60 males and 40 females, with an age range of 18-54 years, and 100 normal weight individuals attending the same department; 60 males and 40 females, as the control group with the same age range. The frequency of skin diseases was significantly high ( $p$ -value  $<0.026$ - $0.00001$ ) in the adult obese group compared with normal BMI individuals, which included the following diseases: acanthosis nigricans (72% versus 1%), planter hyperkeratosis (47% versus 9%), skin tags (58% versus 30%), striae distensae (33% versus 10%), intertrigo (52% versus 6%), hyperhidrosis (30% versus 4%), dry skin (23% versus 10%), and erythrasma (11% versus 3%). While we found other diseases such as hirsutism (20% versus 7.5%), tinea cruris (13% versus 9%), tinea versicolor (11% versus 7%), boils (8% versus 3%) and warts (8% versus 7%), increased among obese individuals, but they were not statistically significant ( $p$ -value  $>0.78$ - $0.05$ ). Other diseases such as dermatitis, psoriasis, leukonychia, and

alopecia areata, were no different in both obese and normal BMI adult individuals.

The present study emphasizes the strong association of skin manifestations and obesity, which reflects the abnormal metabolism mainly insulin resistance, and we also found that the frequency of skin diseases is parallel with the degree of obesity, especially in children.

Acanthosis nigricans (AN) is a major problem among obese individuals, and has been reported in 74%.<sup>1</sup> The present work showed 59.6% among children and 72% among adults, while it was absent in normal weight children, and only 1% in normal weight adults. It has been suggested that hyperinsulinemia is a cause of AN by stimulation of insulin like growth factor 1.<sup>2</sup> Also in a recent Iraqi study, AN has been reported in 68.75% of infertile females with polycystic ovarian syndrome (PCOS).<sup>3</sup> There is a definite association between skin tags and adult obesity.<sup>1</sup> We found skin tags in 13.5% of obese children, and 58% in obese adults, while it was absent in normal weight children, and only 30% in normal weight adults. Obese individuals in both the children and adult groups, showed increased prevalence of planter hyperkeratosis; 48.1% in children and 47% in adult individuals in comparison with normal weight individuals 2% in children and 9% in adults. Only one study has shown an increase in planter hyperkeratosis in obese adults.<sup>1</sup> This study shows a striking association between obesity and striae distensae, both in children and adult individuals compared to normal BMI children and adults. These findings are comparable to previous

**Table 1** - Frequency of skin diseases found in normal BMI, overweight and obese children included in the study.

Skin diseases	Number (%)						Part 1 <i>p</i> values	Part 2 <i>p</i> values
	Normal BMI		Overweight		Obese			
Acanthosis nigricans	0	(0)	26	(27.65)	31	(59.6)	0.0000001	<0.00001
Planter hyperkeratosis	2	(2)	10	(10.6)	25	(48)	0.0000001	<0.00001
Skin tags	0	(0)	1	(1.1)	7	(13.5)	0.000016	<0.0001
Striae distensae	2	(2)	15	(15.95)	18	(34.6)	0.0000003	<0.00007
Intertrigo	1	(1)	3	(3.2)	19	(36.5)	0.0000001	<0.00001
Dry skin	3	(3)	12	(12.8)	24	(46.15)	0.0000001	<0.01
Hyperhidrosis	0	(0)	1	(1.1)	6	(11.5)	0.0001	<0.00001
Dermatitis	3	(3)	6	(6.4)	6	(11.5)	0.11	
Common warts	1	(1)	2	(2.1)	2	(3.8)	0.49	
Leukonychia	10	(10)	15	(15.95)	8	(15.4)	0.4	0.78
Angular cheilitis	1	(1)	1	(1.1)	3	(5.8)	0.09	
<i>Skin infections</i>	1	(1)	2	(2.1)	2	(3.8)	0.49	
Impetigo								
Boils								0.12
Tinea cruris								>0.05
Tinea versicolor								0.322

reports in adults of 42.9%,<sup>1</sup> however, there is no record of striae distensae among obese children. Previous reports demonstrate intertrigo among obese individuals,<sup>4</sup> and we similarly observed this in the present work, as we found intertrigo higher in obese versus normal adult individuals and children. Dry skin was a common problem found more in the obese individuals, mainly affecting cheeks, dorsa of the hands, feet, and legs. This observation was not noticed before, and we could find no clear explanation. We found hyperhidrosis high in obese individuals, when compared to overweight and normal weight children, and similarly found in adult obese in comparison with normal weight individuals. Previous reports confirm this.<sup>5</sup> Previous studies found skin infections, mainly in the form of boils, wart, tinea cruris, and erythrasma increased among obese individuals.<sup>1</sup> While in the present work although they did not reach statistically significant levels, we found more in obese individuals than normal weight individuals, apart from erythrasma, which was significantly high in adult obese individuals. The association between hirsutism and obesity was not clear in the literature, and often hirsutism had been reported to be high in obese females with PCOS.<sup>3</sup> Similarly, in the present work, although it did not reach a statistically significant level, we found more in adult obese females than normal weight females.

The excessive fat deposition that leads to thickening of the fatty layer all over the body deserves the term adipomegaly, rather than obesity as it is more scientific, academic, and more socially and publically accepted.

In conclusion, skin manifestations are a common problem, and important markers of obesity reflecting impaired metabolism, especially acanthosis nigricans, skin tags, and planter hyperkeratosis.

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## Prescribing pattern of angiotensin-converting enzyme inhibitors and beta blockers after acute myocardial infarction

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In recent years, many clinical trials suggested using certain medications such as beta-blockers (BB), angiotensin converting enzyme inhibitors (ACE-I), low dose aspirin, and statins to reduce morbidity and mortality after acute myocardial infarction (AMI). Since the 1980s, we have known the clinical benefits of BB post AMI. Angiotensin converting enzyme inhibitors are also useful in managing asymptomatic and symptomatic left-ventricular dysfunction (LVD), and thus preventing the development of cardiac remodeling process after AMI.<sup>1</sup> Lipid lowering agents, in particular statins decrease the risk of coronary events and total mortality in patients after myocardial infarction.<sup>2</sup> Previous randomized trials illustrate the significant reductions of mortality rate in patients receiving aspirin for secondary prevention after AMI.<sup>3</sup> To evaluate the impact of these clinical trials and evidence based medicine on physician practice pattern, we examined the trends in the use of BB, ACE-I and other medication therapy in patients discharged after AMI. We tried to identify clinical factors associated with ACE-I prescribing patterns.

The data were collected from Al-Watani Governmental Hospital in Nablus, Palestine from January to December 2004. The medical files of patients admitted to the ICU and diagnosed with AMI were reviewed and analyzed. An ECG, enzymes, and symptoms confirmed the diagnosis of AMI. Data obtained from medical files included age, gender, medical history, blood pressure, heart rate, myocardial infarction (MI) type and left ventricular ejection fraction (LVEF). The use of medications at admission and discharge was also

obtained. The major dependent variable analyzed in this study was whether ACE-I or BB was prescribed at hospital discharge or not. The clinical factors associated with ACE-I and BB prescribing were also analyzed. The other 2 important factors in this study considered were MI type and LVEF, due to their important roles in determining appropriate treatment. All data were analyzed using statistical package for social sciences (SPSS) version 11. For statistical significance, chi-square test and cross tabulation were used.

We identified 174 patients with AMI. Twenty-three patients (13.2%) died during hospitalization and were excluded. The mean age of patients was 61.7 years, and the majority was male (72%). Analysis of risk factors predisposing the patients to AMI, among the studied sample, showed that more than half of the patients were men above 60 years old and mostly smokers. Approximately one-third of the patients were hypertensive, and 40% were diabetics. Low dose aspirin and BB were the most common medication prescribed at discharge. On admission, approximately 93% of patients were given both low dose aspirin and heparin as an anticoagulant. Calcium channel blockers were given at a higher rate on admission than at discharge (data not shown). Regarding BB, the rates of prescribing on admission were 79.5% while at discharge were 85.4%, with no statistical difference. Of all the patients included, only 22.4% were prescribed ACE-I at discharge. Neither gender, nor hypertension or the type of MI has a significant effect on prescribing ACE-I at discharge. However, ACE-I prescribing was significantly more common among

diabetic patients, in patients with history of heart failure, and in patients with an LVEF less than 40%. Analyses of medications at discharge showed that patients prescribed calcium channel blockers or digoxin were more likely to receive ACE-I therapy at discharge. In contrast, patients prescribed with BB were less likely to receive ACE-I therapy at discharge. Of all the patients included, 129/151 (85.4%) were prescribed with BB at discharge. The presence of diabetes mellitus (DM) and MI had no significant effect on prescribing BB. However, BB prescribing was significantly more common among patients with an LVEF >40%, in patients with no heart failure, in patients with high blood pressure and in patients prescribed with neither CCB nor ACE-I (**Table 1**). All patients included were prescribed with low dose of 100 mg aspirin; none were prescribed anti-hyperlipidemic statin drugs while 10/151 (6.6%) patients were prescribed CCB. Temporal analysis showed that the prescribing of ACE-I or BB did not change with time during 2004, suggesting that changes in prescribing pattern are usually slow throughout the year.

We undertook this study to determine if, in Palestine, we have practically adopted the established clinical recommendations and evidence-based medicine for treatment after MI. We used physician's prescribing patterns of ACE-I and BB at discharge after MI as the main parameter of assessment, and concluded that there is a low post-infarction prophylactic used of ACE-I while a high post-infarction prophylactic used of BB. Unfortunately, there are no previous studies carried out in Palestine regarding postinfarction prophylactic drugs to compare the current data. Although we found BB

**Table 1** - Influence of various clinical factors on the rate of ACE-I and BB prescribing at discharge after acute myocardial infarction.

Variable	ACE-I prescribed at discharge	ACE-I not prescribed at discharge	BB prescribed at discharge	BB not prescribed at discharge
<b>BP</b>				
High	12/51 (23.5)	39/51 (76.4)	44/51 (86.3)	7/51 (13.7)
Normal	23/100 (23)	77/100 (77)	85/100 (85)	15/100 (15)
<b>DM</b>				
Yes	23/62 (37)	39/62 (62.9)	6/62 (9.7)	56/62 (90.3)
No	12/89 (13.4)	77/89 (86.5)	73/89 (82)	16/89 (18)
<b>LVEF</b>				
< 40%	14/24 (58.3)	10/24 (41.6)	4/24 (6.7)	20/24 (83.3)
> 40%	21/127 (16.5)	106/127 (83.5)	125/127 (98.4)	2/127 (1.6)
<b>CHF</b>				
Yes	13/23 (4.3)	10/23 (43.5)	3/23 (13)	20/23 (87)
No	22/128 (17.2)	106/128 (82.8)	126/128 (98)	2/128 (1.6)
BP - blood pressure, DM - diabetes mellitus, LVEF - left ventricular ejection fraction, CHF - congestive heart failure, ACE-I - angiotensin converting enzyme inhibitors, BB - beta blockers.				

commonly prescribed after AMI in the studied sample, generally, under prescription among patients with MI and heart failure still exists. It is noteworthy that a high percentage of diabetic patients received BB after AMI, agreeing with many studies indicating that BB is more effective in diabetic patients than non-diabetic patients.<sup>1</sup>

We cannot explain the low rate of ACE-I prescribed in the studied patients. It could be that fear from renal functional problems or potassium levels, or fears of hypotension discourage physicians from prescribing ACE-I. Analysis of the effect of age of patients on ACE-I prescribing showed that physicians prescribe this class of drug more commonly to patients above 70 years old compared with younger ones. Again, this is puzzling given the fact that the elderly tend to have higher contraindications to ACE-I than younger patients due to kidney function.

All patients in the study were prescribed low dose aspirin and none were prescribed any other anti-platelet. Statins were not prescribed despite several trials showing their effect in decreasing the risk of coronary events and total mortality in patients after acute MI. The failure to prescribe statins may be due to the unavailability of this class of drug in the hospital. The modern management of patients following MI rests on lifestyle modifications and addressing risk factors such as hypertension, hyperlipidemia, diabetes, and specifically intervening with medications such as ACE-I, BB, statins, and aspirin. We found a large percentage of smokers, and many had other co-morbid conditions that necessitated aggressive post MI prophylactic therapy. Similar studies have taken place in other countries. One carried out in Denmark, found the rate of BB prescribed at discharge after AMI was 67.9%, while prescribing of ACE-I was 35.5%.<sup>5</sup> Another study carried out in the USA in 1998 found the rate of ACE-I prescribing nationwide were 30.7% during the year 1996.<sup>6</sup> Another study carried out in the USA in the state of New York in 1999, found that the ACE-I prescribing rate at discharge after AMI were 34%.<sup>7</sup> A study carried out in Spain in year 2002 found that the rate of prescribing post MI of ACE-I was 32.5% and BB was 50.2%.<sup>8</sup>

In conclusion, we observed that post MI prescribing of BB and low dose aspirin follows the

recommendations of major clinical trials. However, the post MI prescribing of ACE-I and statins do not closely follow the publications of major trials. Focus should be made on the recent updated trials in pharmacological intervention. Non-pharmacological counseling for patients is also needed and should be carried out by clinical pharmacists.

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